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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/571,989	03/13/2006	Michael Kalafatis	CSU-17999	5552

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EXAMINER	
BARNHART, LORA ELIZABETH	

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/571,989	KALAFATIS, MICHAEL	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2009 and 26 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,10,43-49,51 and 112-142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,10,43-49,51 and 112-142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/16/09 has been entered.

Response to Amendments

Applicant's amendments filed 3/26/09 to claims 1, 112, and 113 have been entered. Claims 6 and 7 have been cancelled in this reply. Claims 136-142 have been added. Claims 1-5, 8, 10, 43-49, 51, and 112-142 remain pending in the current application, all of which are being considered on their merits. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 43-49, 51, 120-127, and 129-142 are/remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 43, 120, and 128 are drawn to a composition "adapted for inhibiting thrombin formation," but the source of thrombin is not clear; the claim should point out from where or from what thrombin is formed. There is no antecedent basis for the term "thrombin formation" in the claims, because the compositions are drawn simply to compositions comprising peptides. The relationship between the peptide and some components that generate thrombin is not pointed out in the claim. Similarly, claim 136 is drawn to "a peptide for direct binding to thrombin," but there is no thrombin recited in the claimed composition; it is not clear whether thrombin is part of the claimed composition or not. Clarification is required. Because claims 44-49, 51, 121-127, 129-135, and 137-142 depend variously from indefinite claims 43, 120, 128, and 136 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Regarding the rejection of record, applicant alleges that he is not required to identify physical properties of the composition that account for the function (Reply, pages 14-15). Applicant alleges that the examiner has misread the claims because they describe an inhibitor of thrombin formation and therefore do not imply any thrombin formation (Reply, pages 15-16). These arguments have been fully considered, but they are not persuasive. The basis of this rejection is the fact that the claims refer to components that are not part of the claimed composition and have no clear structural or physical association with the claimed composition. In order to inhibit thrombin formation, it is respectfully submitted that thrombin formation must be a possibility. Applicant appears to be attempting to describe a phenomenon that occurs when the

instant composition is placed into an environment in which thrombin formation may occur, but such discussion confounds the issue of the scope of the instant claims, which are drawn to compositions and to compositions only.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 8, 10, 43-49, 51, and 112-142 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hortin (1990, *Blood* 76: 946-952; reference AM on 3/13/06 IDS) taken in view of Pittman et al. (1994, *Biochemistry* 33: 6952-6959; reference AO on 3/13/06 IDS), Bakker et al. (1994, *Journal of Biological Chemistry* 269: 20662-20667), and Ramabhadran (1994, *Pharmaceutical Design and* Development, Ellis Horwood, New York NY, pages 40, 42, and 43).

Hortin teaches that the complete sequence of human coagulation factor V (hereafter "Factor V") was known at the time of the invention and that said sequence includes the sequence DYDYQ (and, therefore, DYDY; page 946, column 1, paragraph 2; and Figure 6 at page 950, e.g.). Hortin teaches that Factor V is sulfated *in vivo* and suggests that the tyrosine residues at positions 696 and 698 are among the residues that are sulfated (page 950, column 2). Hortin speculates that thrombin binding to Factor V may be mediated by binding to these sites (page 951, column 1); this conclusion is based in part on the fact that sulfation of tyrosine residues in other proteins modulates their direct binding to thrombin (page 946, column 2). Hortin teaches a solution comprising Factor V (page 946, column 2, last paragraph).

Hortin does not teach any fragments of Factor V, e.g. the tetrapeptide DYDY or the pentapeptide DYDYQ. Hortin does not exemplify a peptide in which one or both of the tyrosines in the DYDY or DYDYQ motif are sulfated.

Pittman teaches that inhibiting sulfation of Factor V inhibits its procoagulant activity (page 6955, column 1, under "Sulfation is required..."). Specifically, Pittman teaches that Factor V must be sulfated to undergo binding and subsequent cleavage by thrombin (page 6956, column 1; and Figure 3B). Pittman concurs with Hortin that tyrosines 696 and 698 are likely candidates for the sulfation (page 6957, column 1, under "Discussion"). Pittman also teaches methods for sulfating proteins (pages 6953 and 6954).

Bakker teaches that the portion of Factor V heavy chain required to bind thrombin is the C-terminal 27 amino acids thereof, which comprises the DYDYQ motif

(see Table II at page 20665 and page 20664, column 1, first full paragraph). Bakker further teaches that these 27 amino acids are responsible for the binding of Factor V to prothrombin (page 20667, column 1, first full paragraph).

Ramabhadran teaches that small peptides (i.e., up to 50 amino acids) may be made in high yield and with high purity by synthesizing them chemically from their constituent amino acids (page 43). Ramabhadran teaches that chemically synthesized peptides are useful in the laboratory as drugs (page 43, third full paragraph).

The person of ordinary skill in the art would have had a further reasonable expectation of success in producing short peptides including tyrosine residues 696 and 698 because Hortin teaches that the entire sequence of Factor V was known at the time of the invention and because Ramabhadran teaches that peptides of up to 50 amino acids in length and with a given sequence may be chemically synthesized. The skilled artisan would have been motivated to produce such peptides because Bakker teaches that the C-terminal portion of Factor V heavy chain, which comprises tyrosine residues 696 and 698, is the domain required to bind prothrombin; the skilled artisan would have been motivated to determine which of these 27 residues is necessary for the interaction and which are not. Furthermore, sulfating these residues would have constituted routine experimentation on the part of the skilled artisan, since Pittman teaches methods for doing so. The skilled artisan would have been motivated to sulfate the tyrosine residues because Pittman and Horton both teach that they may be sulfated *in vivo*, because Bakker teaches that these residues are within a domain that binds prothrombin, and because Pittman teaches that Factor V must be sulfated to bind thrombin. Therefore,

the skilled artisan would have endeavored to learn whether the tyrosine residues in the 27-amino acid peptide of Bakker need be sulfated to bind prothrombin. In light of the practical teachings and predictions of the art, the determination of the peptide sequence and sulfation pattern would have constituted routine experimentation at the time of the invention. See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

The skilled artisan would have had a reasonable expectation that peptides made as suggested by the art as set forth above would inhibit thrombin activity because Hortin teaches that Factor V is bound and cleaved by thrombin, Bakker teaches that the C-terminal 27 amino acids of Factor V are the portion involved in binding thrombin, and Pittman and Horton teach that residues 696 and 698 are likely required for thrombin binding. See *KSR*.

A person of ordinary skill in the art would have had a reasonable expectation of success in sulfating either or both of the tyrosine residues at positions 696 and 698 within Factor V because Hortin and Pittman both teach that these residues are within consensus sequences for sulfation. The skilled artisan would have been motivated to sulfate one or both of these residues in Factor V because Pittman teaches that Factor V is not active unless it is sulfated.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to produce peptides using the method of Ramabhadran that correspond to various portions of the 27 amino acids of Factor V taught by Bakker to be involved in binding thrombin in order to determine which portions of this fragment are necessary for thrombin binding. It would have been further obvious to sulfate one or

more of the tyrosine residues within the resulting peptide because Pittman teaches that sulfation is required for activity and teaches methods for sulfating proteins.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant alleges that the fact that Pittman indicated that the role of the sulfation sites was not fully understood constitutes a teaching away from the instant invention (Reply, page 31), but the examiner disagrees. Pittman suggested a link between sulfation and Factor V's ability to inhibit thrombin formation; this suggestion represents a clear invitation to experiment and an indication that such a link is possible and even probable. It is not clear how following the explicit direction provided by the prior art constitutes innovation.

Applicant's reply suggests that the age of the references somehow disqualifies them from being included in an obviousness rejection (Reply, pages 30-33). Contentions that the reference patents are old are not impressive absent a showing that the art tried and failed to solve the same problem notwithstanding its presumed knowledge of the references. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977).

Applicant alleges that Bakker teaches away from the invention (Reply, page 32), but it is respectfully submitted that applicant has misinterpreted the teachings of Bakker. The Va_{NO} of Bakker that is discussed in the passage referenced by applicant (page 20665 of Bakker and page 24 of the reply) is not a peptide that consists of the last 27 amino acids of Factor Va, but rather a peptide that includes the entire sequence of

Factor Va except for these last 27 amino acids. "[T]he heavy chain of factor Va_{NO} had a slightly increased electrophoretic mobility, indicating the loss of a small peptide … from the heavy chain" (page 20663, column 2, third full paragraph). Bakker teaches that when the C-terminal 27 amino acids are removed from Factor Va, the resulting peptide (Va_{NO}) activates thrombin more effectively than does native Factor Va; the reply appears to stipulate to the fact that Va_{NO} is a less effective thrombin inhibitor than is Factor Va. The skilled artisan would have concluded from these teachings that these C-terminal 27 amino acids possess an activity that inhibits thrombin activation. This C-terminal portion would therefore have been a region of interest to artisans seeking thrombin inhibitors. The fact that Bakker was not concerned with the exact problem that the instant application addresses does not constitute a teaching away. Patents are relevant as prior art for all they contain. A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art. See M.P.E.P. §2123.

Applicants urge that none of the references teaches the claimed peptide (Reply, pages 33-34). However, none of the references is applied alone; the references are applied in combination and in view of the state of the art at the time of the invention, and the claimed invention becomes obvious when the references are considered together as a whole rather than each alone.

Applicant alleges that the references do not teach binding between Factor V and thrombin (Reply, pages 34-35), but the examiner submits that the instant claims are drawn to peptides and peptides only. As set forth in the rejection, the prior art provides

motivation to identify the portion of Factor V involved in thrombin cleavage and activation (see Pittman and Hortin, both of which establish a link between Factor V sulfation and thrombin activation). Hortin teaches that sulfation of tyrosine residues in other proteins modulates their direct binding to thrombin (see page 946, column 2) and explicitly contemplates a direct interaction of Factor V and thrombin. Again, it is not clear how following the explicit direction provided by the prior art constitutes innovation.

Applicant alleges that the art was unpredictable at the time of the invention (Reply, pages 35-37), but the examiner disagrees. Obviousness does not require absolute predictability; however, at least some degree of predictability is required. See M.P.E.P. § 2143.02. Applicant implies that the prior art must have explicitly envisaged the exact invention to be considered "predictable," which is incorrect.

Applicant again alleges the presence of objective evidence of nonobviousness (Reply, pages 37-39), but the examiner maintains that applicant's reply does not clearly indicate what aspects of this data are unexpected; rather, the reply refers to the figures generally. The burden is on applicant to explain data, particularly pointing out that it represents results that are both unexpected and significant. See M.P.E.P. § 716.02(b).

In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court wrote, "Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility" (see *KSR* at 1396). Surely applicant cannot intend to argue that "routine experimentation" differs substantially in meaning from "advances that would occur in the

ordinary course," as at page 51 of the reply. "The person of ordinary skill is also a person of ordinary creativity, not an automaton" (see *KSR* at 1397). Applicant alleges that *KSR* established that a demonstration of a teaching, suggestion, or motivation provides a "helpful insight" in determining obviousness (citing *KSR* at 1396). In the paragraph of the decision immediately after the one referenced by applicant, the Court points out, "Helpful insights, however, need not become rigid and mandatory formulas … The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way" (ibid.). The gist of *KSR* is that no explicitly stated motivation for combination need be present in the art for a proper rejection under 35 U.S.C. § 103 if the art fairly suggested the modifications necessary to arrive at the claimed invention.

Nonetheless, the examiner indeed provided a motivation and a showing of reasonable expectation of success for the person of ordinary skill in the art to combine the teachings of the prior art, as detailed above. Applicant has provided no evidence or convincing argument that true innovation led to the claimed invention and that skilled artisans could not have arrived at the claimed composition at the time of the invention, given the advanced state of the art as set forth in the rejection.

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP

714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651